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Time Course of Cardiac Structural, Functional and Electrical Changes in Asymptomatic Patients After Myocardial Infarction: Their Inter-Relation and Prognostic Impact

Peter Gaudron, MD,* Ingrid Kugler, MD,* Kai Hu, MD,† Wolfgang Bauer, MD,†
Christoph Eilles, MD,‡ Georg Ertl, MD†

Heidelberg, Würzburg and Regensburg, Germany

OBJECTIVES We prospectively studied the relationship between left ventricular (LV) dilation, dysfunction, electrical instability and death in patients after a first myocardial infarction (MI) without symptoms of heart failure and ischemia.

BACKGROUND Mechanisms linking LV dysfunction and sudden death in patients after MI remained controversial.

METHODS Left ventricular volumes, hemodynamics, electrocardiogram and 24-h Holter recordings were sequentially obtained between two days and seven years after MI. Left ventricular catheterization and coronary angiography were performed, and revascularization was performed if appropriate.

RESULTS Death occurred in 16 (12%) of the 134 patients included; it was of cardiac origin in 14 (88%) and sudden in origin in 12 (75%) patients. Of 37 (28%) patients with LV dilation, 12 died (32%); four patients (5.8%) died in the group without dilation. Left ventricular dilation was closely related to signs of electrical instability, as indicated by a significant correlation between end-diastolic LV volume index, Lown score ($r = 0.98$, $p < 0.0001$) and QTc prolongation ($r = 0.998$, $p < 0.01$), respectively.

CONCLUSIONS Patients with progressive remodeling are at increased risk of sudden death in chronic MI. Cardiac electrical instability is closely related to progressive LV dilation. Parameters of electrical instability and remodeling are predictors of sudden death. The findings suggest that remodeling might serve as a link between dysfunction, electrical instability of the heart and sudden death after MI. (J Am Coll Cardiol 2001;38:33–40) © 2001 by the American College of Cardiology

Patients with heart failure are at high risk for sudden death (1,2). The relationship between the degree of dysfunction, occurrence of ventricular arrhythmias and the risk of sudden death (2,3) and the mechanism leading from dysfunction to sudden death are not clear. Identification of patients with left ventricular (LV) dysfunction who are at increased risk for sudden death and the potential influence of therapy on these patients is difficult to assess. Ejection fraction has low specificity (4); predictors of electrical instability are limited by a high false-positive rate and a positive predictive value of <30% (5–7). It is controversial whether or not sudden death and severity of heart failure are directly related (4,8–10) since their occurrence is not temporally related, and patients with less severe heart failure had a greater risk of sudden death in the Vasodilator-Heart Failure Trial (V-HeFT) patient population (11). Left ventricular volume, as a hallmark of the remodeling process (12), is one of the most powerful predictors of long-term survival in patients after myocardial infarction (MI) (13) and contributes to progressive dysfunction (14,15). This prospective study, which was conducted in patients who were asymptomatic after MI, was designed to analyze the process leading from dysfunction to death in individual patients. We tested the hypothesis that progressive LV dilation is closely related to electrical instability and may serve as a link between dysfunction and death.

METHODS

Patient selection. From January 1987 to January 1990, 416 patients were admitted to our intensive care unit with acute MI confirmed by electrocardiogram (ECG) and creatine kinase enzymes. Thrombolytic therapy was administered if not contraindicated according to currently accepted criteria. Of these patients, 175 matched our inclusion criteria (age of ≤70 years, first MI and signed informed consent). Patients were excluded with clinical signs of heart failure or cardiogenic shock in the first week after MI, unstable angina, life-limiting noncardiac disease, conditions precluding cardiac catheterization or exercise testing or delayed (>6 days) hospital admission. Twenty-four patients refused to partic-

From the *II.Medizinische Universitätsklinik, Klinikum Mannheim der Universität Heidelberg, Heidelberg, Germany; †Medizinische Universitätsklinik Würzburg, Würzburg, Germany; and the ‡Department of Nuclear Medicine, Universität Regensburg, Regensburg, Germany. Supported by grant SFB 355/B9 from the Deutsche Forschungsgemeinschaft, Universität Würzburg, Würzburg, Germany and the Forschungsfond der Falkutät für Klinische Medizin Mannheim, Universität Heidelberg, Heidelberg, Germany.

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Abbreviations and Acronyms

ANP = atrial natriuretic peptide
BUN = blood urea nitrogen
ECG = electrocardiogram
LV = left ventricle/ventricular
MI = myocardial infarction
SDANN = standard deviation of the average NN interval
SDNN = standard deviation of the NN interval

ipate, and an additional 17 patients were excluded who did not adhere to the follow-up protocol.

Study protocol. The protocol was approved by the Institutional Committee on Human Experimentation and in accordance with the Helsinki Declaration. Four days (two to six days), four weeks (three to five weeks), six months (five to eight months), 1.5 years (16 to 20 months) and three to seven years (58 to 86 months) after admission, 12-lead ECGs and 24-h Holter were obtained. Additionally, LV end-diastolic and end-systolic volumes and ejection fraction were measured, and right heart catheterization was performed simultaneously at rest. Four weeks after admission, coronary angiography and biplane cineangiography were performed in all patients. Patients were fasting the night before and were off medication for the previous 24 h. The patients' therapy remained the responsibility of the attending physician.

LV volumes and ejection fraction. Gated blood pool radionuclide ventriculograms were sequentially obtained in each patient as described in detail elsewhere (15). In brief, erythrocytes were labeled "in vivo" by 15 to 20 mCi technetium-99m pertechnetate. The cardiac cycle was gated into eight frames triggered by ECG and images obtained by a rotating gamma camera (gated single photon emission computed tomography) followed by standard planar radionuclide ventriculography for determination of global LV ejection fraction.

Hemodynamics and angiography. Coronary angiography in multiple views and biplane LV angiography were performed by a Sones procedure. Infarct size was quantitated as the percentage of akinetic and dyskinetic segment length of the total end-diastolic circumference of the biplane contrast LV angiogram (15). Perfusion of infarct-related coronary artery was assessed according to the Thrombolysis In Myocardial Infarction (TIMI) trial (16). An operator blinded to the other measurements performed these measurements. Right heart catheterization was performed and cardiac output measured by a Swan-Ganz thermodilution catheter (7F Edwards, Braun-Melsungen AG, Melsungen, Germany) and a Siemens Sirecust 404-1A (Erlanger, Germany) computer by three repeated injections of 10.0 ml iced saline. Left ventricular stroke volume was calculated and related to body surface area as stroke volume index. For right heart catheterizations performed separate from angiography, a transcutaneous ("Seldinger") approach was used.

Rhythm analysis. HOLTER ANALYSIS. Methods of Holter recordings matched the guidelines of the American Heart Association and European Society of Cardiology (17,18). Automatic Holter analysis included 24-h heart rate variability and average, maximum and minimum heart rate using the ELA Medical System (München, Germany). Correctness of the automatic measurements was validated by comparison of automatic with visual analysis of 10 randomly selected 24-h recordings. Sensitivity and specificity of the automatic measurements were 100% and 95%, respectively. Arrhythmias were visually assigned and quantitated. Intra- and interobserver variability was low, as indicated by positive correctness of 98%. Ventricular arrhythmias were categorized according to the modified Lown classification (19), and each Lown grade was assigned to a score number from zero to 7. Deviation of normal RR intervals (resulting from sinus node depolarizations, standard deviation of the NN interval [SDNN], ms, ELA Medical System) were determined after manual correction of automated analysis for supraventricular and ventricular premature beats or artifacts, respectively (18). Standard deviation of the averages of NN intervals in all 5-min segments of the entire 24-h recording (SDANN [ms]) was determined. Standard deviation of the averages of NN intervals and SDANN were determined following guidelines of the European Society of Cardiology (18).

QT analysis. QT duration, as the interval from the Q-wave deflection to the end of the T-wave, was measured in high quality 24-lead surface ECG recordings. The final value is the average of three measurements in each of the 12 leads. These measurements were corrected for heart rate (RR interval) and expressed as QTc using the equation: $QTc = QT/RR^{-0.5}$ (20). A QTc duration >0.45 s was considered to be prolonged (5). To assess dispersion of QTc duration within the 12-lead ECG, the difference between the largest and smallest QTc duration was calculated online after digitization of original ECG tracings using a calibrated digitizing tablet (Numonics, Montgomeryville, Pennsylvania) and the Sigma Scan Pro (SPSS ASC GmbH, Erkrath, Germany) software package by a person blinded to all other data.

Analysis of deaths. The dates of all deaths were documented, and details of the events at the time of death and the preterminal conditions of the patient were obtained from family members, friends or the treating physician. Sudden death without prodromes was defined according to the currently accepted criteria as death that occurred within 1 h of the onset of acute symptoms. It was assumed to be cardiac if no other explanations were found. Sudden death with prodromes was defined accordingly if symptoms such as new or worsening chest pain, palpitations, dyspnea or weakness occurred within 24 h before death.

Laboratory measurements. Thirty minutes after placement of a venous line between 10 AM and 2 PM and supine rest, blood samples were drawn for standard laboratory tests. Additional blood was collected into prechilled tubes, cen-

Table 1. Baseline Clinical Characteristics and Angiographic Findings

	Survivors (n = 118)	Nonsurvivors (n = 16)	p Value
Gender (M/F)	113/5	14/2	NS
Age	55.3 ± 0.8	61.1 ± 1.8	0.0103
Thrombolytic therapy on admission	50 (42.4%)	6 (37.5)	NS
Characterization of infarction:			
Anterior	45 (38.1%)	5 (31.3%)	NS
Lateral	10 (8.5%)	0	
Inferior	59 (50%)	10 (62.5%)	NS
Q-wave	61 (51.7)	9 (56.3)	NS
Wedge pressure (mm Hg)	10.4 ± 0.5	15.0 ± 1.7	<0.05
Right atrial pressure (mm Hg)	5.7 ± 0.4	8.2 ± 1.5	<0.05
Ventriculographic infarct size (%)	11.8 ± 1.2	24.0 ± 3.2	0.0431
Percent narrowing of MI-related artery	74.7 ± 3.0	81.5 ± 6.8	<0.0001
TIMI grade* of MI-related artery	1.84 ± 0.11	1.45 ± 0.28	NS

Values are mean ± SEM. *TIMI grade: "0" = no flow; "1" = minimal perfusion; "2" = partial perfusion; "3" = complete perfusion.
MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

trifuged at 4°C at 2,500 rpm for 12 min and plasma stored in a polypropylene tube at −20°C for renin activity, atrial natriuretic peptide (ANP) and catecholamines measurements. Plasma catecholamines were measured by high-pressure liquid chromatography. Plasma renin activity and ANP were measured by radioimmunoassay using commercially available antibodies.

Statistical analysis. Clinical characteristics at baseline (Table 1) and the last visit (Table 2) between survivors and nonsurvivors were compared by Student *t* test. Two-way analysis of variance was performed to test for differences over time and between survivors and nonsurvivors. The survival curves were compared by the log-rank test. Age, ventriculographic MI size, percent narrowing of MI-related artery, ejection fraction, stroke volume index, LV end-diastolic and end-systolic volume index, mean pulmonary capillary wedge pressure, mean right atrial pressure, maximum, minimum and mean heart rate (Holter), Lown score, QTc dispersion, maximum QTc duration, serum creatinine, blood urea nitrogen (BUN), plasma ANP and a discriminate score "discscore" were preselected to have independent effects on survival. "Discscore" was derived from multivariate discriminant analysis in a previous publication (15) from the following: ejection fraction on day 4, ventriculographic MI size, MI location, stroke index at day 4 and the rate of arteriographic contrast flow in the MI artery (TIMI grade). These variables were significant predictors of progressive, limited or no LV dilation and classified 89% of the patients correctly. Using the discriminant coefficients, a "risk equation" can be provided (15). The contribution of the discscore and other covariates was investigated by stepwise logistic regression (21). This was achieved by a standard approach for multivariate analysis using stepwise automatic logistic regression (SAS software package 6.12; SAS Institute, Cary, North Carolina). For the multivariate procedure, variables were used only if they showed a p value <0.05 in univariate analysis. A value of $p < 0.05$ indicated a significant difference. Results are presented as mean ±SEM.

RESULTS

Survival curves. Of 134 patients, 16 (12%) died. Deaths were considered cardiac in 14 (88%) patients, sudden without preceding symptoms in 11 (69%) and with preceding symptoms in one patient. Two patients died of noncardiac reasons (cerebral bleeding, thyroid C-cell carcinoma). During follow-up, 37 patients (28%) developed significant LV dilation, defined as end-diastolic volumes larger than the mean value of normal end-diastolic volume (75 ml/m^2) plus two standard deviations (26 ml/m^2); the normal value was obtained from 18 persons without cardiac disease. Figure 1 shows the cumulative survival curves; four deaths occurred in the group without dilation, 12 deaths in the group with dilation. Mortality in the group with LV dilation (23.4%) was significantly higher ($p = 0.00018$) than it was in the group without dilation (5.8%).

Clinical characteristics, medication and laboratory findings. Table 1 shows that nonsurvivors were older, that MI size was larger and that percent narrowing of the infarct-related coronary artery was greater. All other variables, including laboratory tests (not shown), MI-related artery and number of affected coronary arteries, were similar in both groups. Perfusion of the MI-related artery tended to be worse in nonsurvivors. At last visit (Table 2), pulmonary wedge pressure, plasma creatinine, BUN and ANP were significantly higher in nonsurvivors compared with survivors. All other characteristics were similar in both groups, including serum electrolytes (not shown).

Volumes and hemodynamics. Time course of LV end-diastolic volume is shown in Figure 2A. End-diastolic (Fig. 2A) and end-systolic (not shown) volume progressively increased in nonsurvivors significantly more than it did in survivors. Ejection fraction (Fig. 2B) in nonsurvivors was always lower than it was in survivors; stroke volume index (Fig. 2C) normalized after four weeks but fell thereafter. Wedge pressure was elevated in nonsurvivors at last visit (Table 2).

ECG. Mean heart rate was higher in nonsurvivors than it was in survivors at four days but was similar in both groups during further observation (Fig. 3B). A clear sinus-wave shaped curve was observed at maximum heart rate in survivors at anytime (Fig. 3A). Maximal heart rate was higher in nonsurvivors than it was in survivors at four days, and the typical sinus curve was lost (Fig. 3A). In nonsurvivors, maximum heart rate sharply increased at 0.5 years (Fig. 3A). Figure 2D shows that maximum QTc was elevated after MI and remained increased in nonsurvivors while it decreased 0.5 years after infarction in survivors. Dispersion

Table 2. Clinical Characteristics, Interval Revascularization, Drug Therapy and Laboratory Findings at Last Visit in Survivors and Nonsurvivors

	Survivors (n = 118)	Nonsurvivors (n = 16)	p Value
Clinical characteristics:			
Hypertension	24 (20%)	2 (13%)	NS
Diabetes	6 (5%)	1 (6%)	NS
Current smoking	47 (40%)	6 (38%)	NS
High cholesterol (>220 mg/dl)*	66 (56%)	10 (63%)	NS
Recurrent infarction	14 (12%)	2 (13%)	NS
New York Heart Association functional class:			
I	66 (56%)	12 (75%)	NS
II	37 (31%)	3 (19%)	NS
III	0	1 (6%)	
IV	0	0	
Canadian Heart Association angina class:			
I	83 (70%)	14 (88%)	NS
II	18 (15%)	2 (12%)	NS
III	0	0	
IV	0	0	
Pulmonary wedge pressure (mm Hg)	10.3 ± 0.7	22.0 ± 3.4	$p < 0.05$
Interval revascularization:			
PTCA	7 (6%)	1 (6%)	NS
Coronary bypass surgery	4 (3%)	1 (6%)	NS
Drug therapy:			
ACE inhibitors	19 (16%)	3 (19%)	NS
Antiarrhythmic drugs	7 (6%)	1 (6%)	NS
Warfarin	33 (28%)	6 (38%)	NS
Acetylsalicylic acid	58 (49%)	7 (44%)	NS
Beta-blockers	56 (48%)	4 (25%)	NS
Calcium channel blockers	36 (31%)	3 (19%)	NS
Digitalis	19 (16%)	3 (19%)	NS
Diuretics	13 (11%)	2 (13%)	NS
Nitrates	69 (58%)	5 (40%)	NS
Laboratory findings:			
Serum creatinine (mg/dl)†	1.05 ± 0.18	1.66 ± 1.07	$p = 0.0386$
BUN (mg/dl)‡	17.3 ± 4.3	27.6 ± 13.1	$p = 0.0035$
Serum digoxin	1.6 ± 0.2	1.4 ± 0.2	NS
Plasma norepinephrine (pg/ml)	206 ± 128	182 ± 111	NS
Plasma renin (ng/ml/h)	4.6 ± 10.5	5.2 ± 4.5	NS
Plasma ANP (pg/ml)	51 ± 32	129 ± 34	$p < 0.0001$

Values are mean ± SEM. *For conversion to pmol/l multiplication factor = 0.02586; †for conversion to pmol/l multiplication factor = 88.4; ‡BUN, for conversion to mmol/l multiplication factor = 0.357.

ACE = angiotensin-converting enzyme; ANP = atrial natriuretic peptide; BUN = blood urea nitrogen; PTCA = percutaneous transluminal coronary angioplasty.

of QTc (Fig. 2E) decreased over time but was always significantly higher in nonsurvivors than it was in survivors. Lown classification (Fig. 2F) was similar in survivors and nonsurvivors early after infarction but significantly increased in nonsurvivors over time. There is a highly significant positive correlation between LV end-diastolic volume and QTc duration ($r^2 = 0.998$, $p = 0.0030$) or Lown score ($r^2 = 0.980$, $p < 0.0001$), respectively. The SDNN in survivors increased beyond four days and remained stable after 0.5 years following MI while it was reduced initially, increased after four days but fell again until three years after MI in nonsurvivors (not shown). The SDANN in survivors was depressed four days after MI and showed a tendential increase thereafter. The SDANN in nonsurvivors initially was depressed but showed a significant increase until six months after MI and remained stable thereafter (not shown).

Multivariate analysis of predictors of death. The statistical procedure selected discscore, maximal heart rate, creatine, stroke volume index and pulmonary wedge pressure as early predictors of death. Intermediate predictors of death included parameters of cardiac electrical instability (QTc dispersion, Lown score, maximal heart rate and QTc) and end-systolic volume. Late predictors of sudden death were end-systolic volume and maximum QTc duration.

DISCUSSION

A major result of this prospective study was that patients who die in the chronic course after MI show progressive LV dilation, dysfunction and electrical instability. Morphologic, hemodynamic and electrical changes were closely interrelated, and most deaths occurred suddenly. Association of higher mortality with dilation is in accordance with a

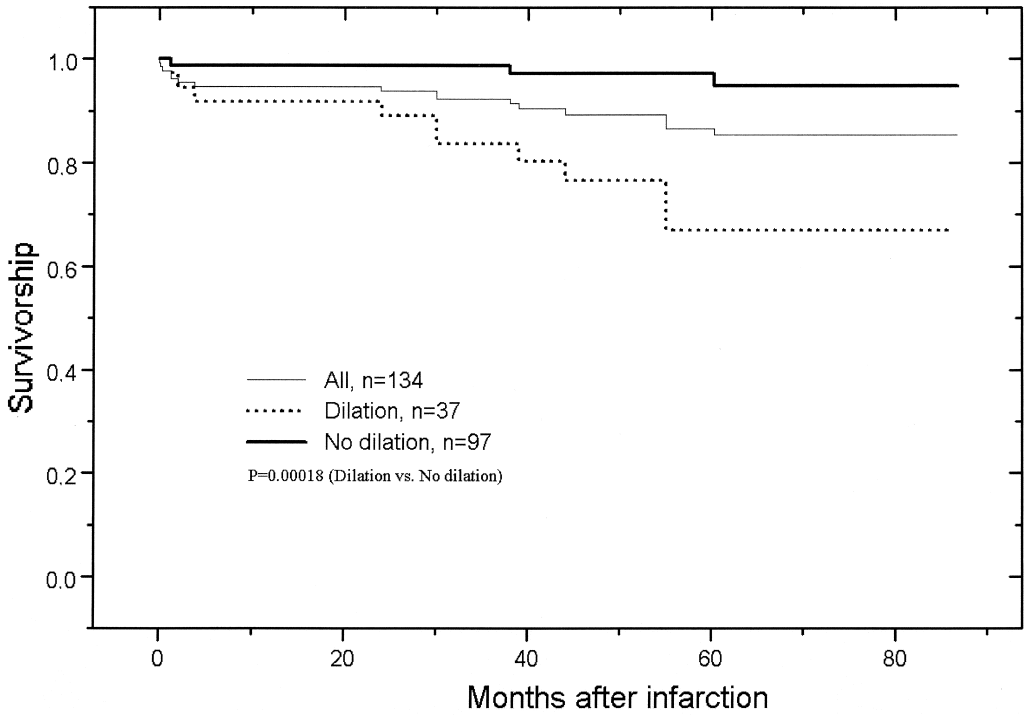

Figure 1. Cummulative survival curves for all patients in the study (**solid line,** n = 134), for patients without left ventricular dilation (**solid bar,** n = 97) and for patients with left ventricular dilation (**dotted line,** n = 37). Mortality was significantly (p = 0.00018) higher in patients with left ventricular dilation (32%) compared with patients who did not show left ventricular dilation (5%).

previous study that has shown that a single measurement of LV volume is a strong predictor of prognosis (12). This study suggests (in concert with previous data [13]) that this single measurement is part of a progressive process. It supports (along with observations of others [14]) the concept that LV dilation after MI is both a compensatory mechanism to restore stroke volume and a pathomechanism for progressive dysfunction. The severity of circulatory dysfunction is reflected by an increased plasma creatinine, BUN and ANP at last visit. Heart rate abnormalities associated with increased risk for sudden death were detectable early after MI. Later on (>4 weeks, ≤3 years), pathological dispersion and duration of QTc interval and Lown classification were identified as predictors of sudden death by multivariate analysis. Thus, the present prospective study demonstrates that gradual development of electrical instability precedes sudden death in this population. Patients who died were also characterized early on by more severe dysfunction. However, there was no significant relation between arrhythmias and ejection fraction. In contrast and most importantly, LV volume correlates significantly with Lown classification and QTc duration. The unique quantitative relation between ventricular volume and characteristics of ventricular arrhythmias suggests a mechanistic interdependence. Mechanical variables in general were predictors of survival early after the infarct, while electric and autonomic variables gained their predictive value later. The clinical relevance of these observations needs to be tested prospectively. In addition, the prevalence of ventricular arrhythmias increases in parallel to symptoms of heart failure (3,10). This study extends these observations to asymptomatic patients with LV dysfunction and shows that hemodynamic and structural (ventricular dilation and remodeling) abnormalities precede electrical abnormalities and predict sudden death. However, a common prior cause of both mechanical and electrical deterioration may not entirely be excluded by these data. In addition, some imbalance of drugs used in survivors and nonsurvivors, although not statistically significant, may have influenced the results.

Arrhythmias: potential mechanisms. The rate of sudden death is very high in this study compared with others. The reliability with regard to observations of sudden death has been questioned recently (22). However, the close contact with the patients and the observation that frequency and complexity of ventricular arrhythmias increased gradually suggests death by an arrhythmia. Plasma levels of electrolytes and the use of diuretics, digitalis and antiarrhythmic drugs was similar, and we tried to prevent ischemic events at the beginning and during the study. If ischemia was present, coronary angiography was repeated and, if appropriate, percutaneous transluminal coronary angioplasty or bypass surgery was performed. There was no evidence for silent ischemia in 24-h ECG recordings. Thus, systematic prevention of ischemic events and exclusion of patients in hemodynamic instability or heart failure immediately after the infarct may have excluded patients at risk for events other than sudden death. Elevated mean heart rate during the first week after MI and elevated maximum heart rate at 0.5 years in nonsurvivors compared with survivors is com-

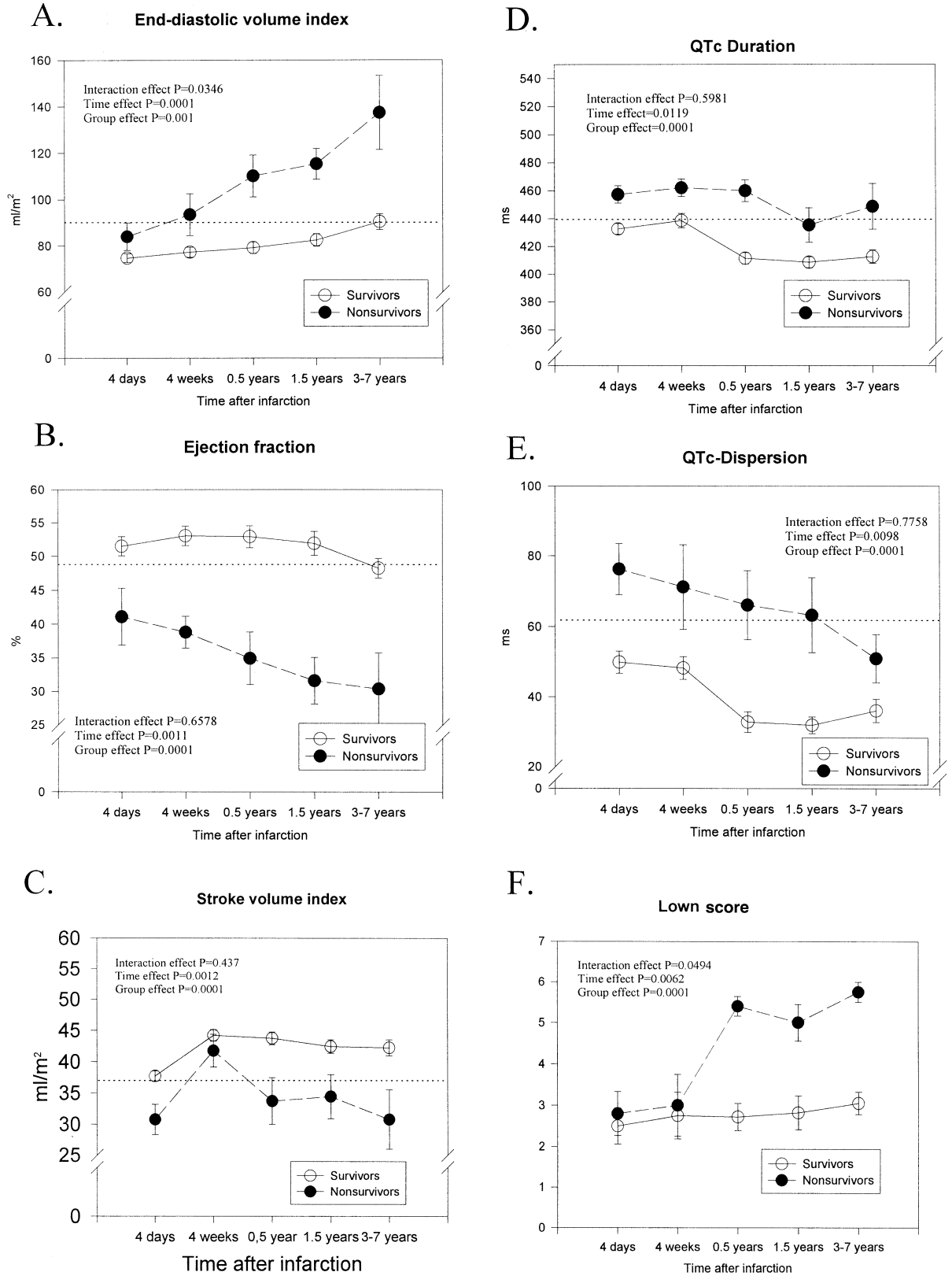

Figure 2. **(A)** Shows that end-diastolic volume increased significantly and progressively and in nonsurvivors more than in it did in survivors. Left ventricular ejection fraction was decreased in nonsurvivors **(B)**. Stroke volume index increased in survivors while it was depressed in nonsurvivors except at four weeks after infarction **(C)**. **(D)** Shows that QTc duration decreased at and after 0.5 years after myocardial infarction in survivors but increased in nonsurvivors. QTc dispersion was decreased in survivors versus nonsurvivors **(E)**. Lown score in survivors remained unchanged over time **(F)**. Lown score significantly increased in nonsurvivors. Lown score 1 to 7 denotes: Lown grade 0; I; II; IIIa; IIIb; IVa; IVb. Values are mean ± SEM. The **horizontal dashed lines** indicate the upper **(A,D,E)** or lower **(B,C)** limit of normal for the respective value.

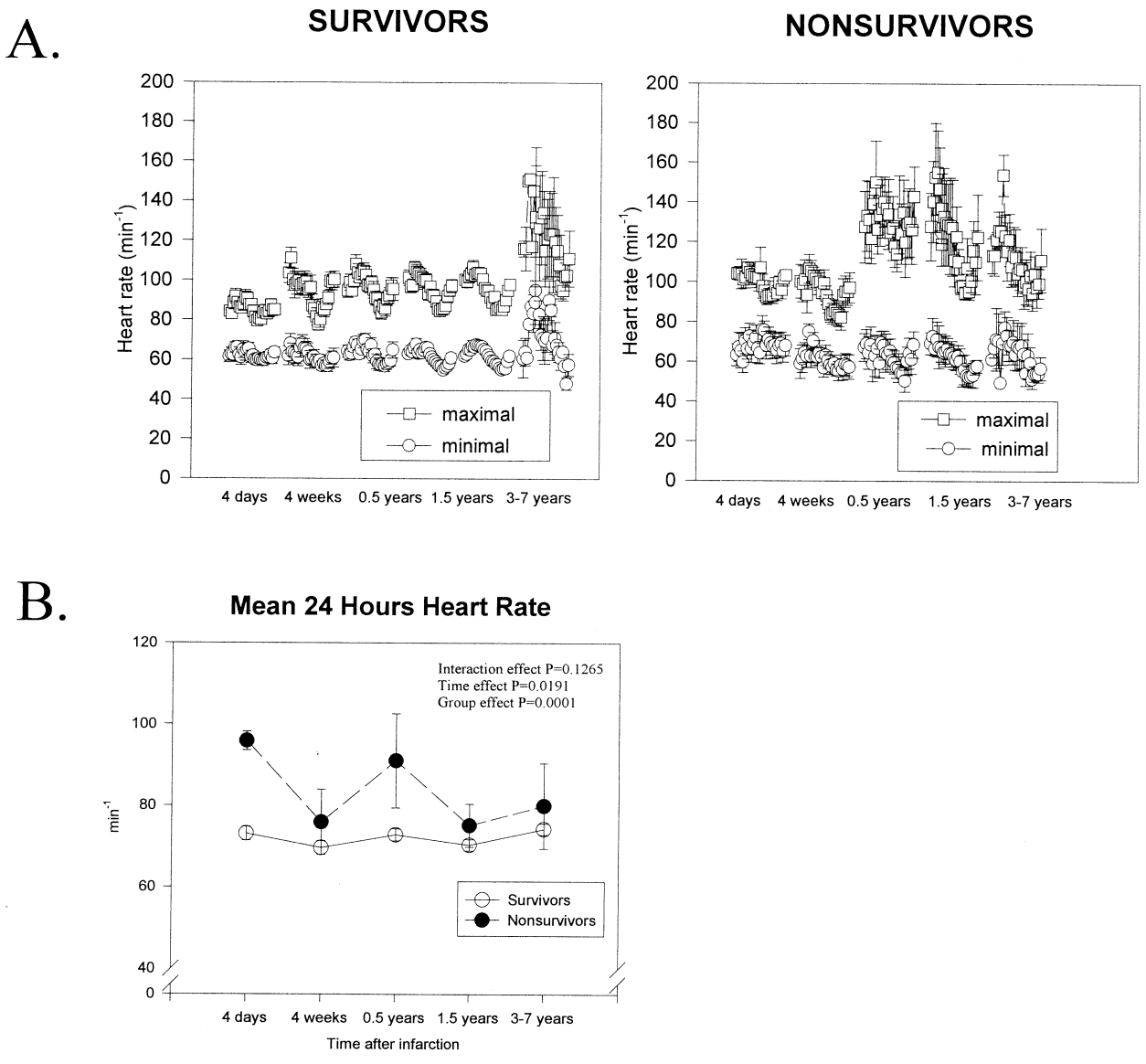

Figure 3. Maximum and minimum heart rate **(A)** and mean heart rate in survivors and nonsurvivors **(B)**.

patible with early autonomic disturbance, normalization during subacute MI and recurrence of parasympathetic withdrawal and sympathetic overactivity at 0.5 years after MI. After this time interval, Lown score and maximum QTc duration indicated electrical instability. Left ventricular remodeling after MI includes hypertrophy and fibrosis in noninfarcted myocardial regions (23) and thinning and elongation (i.e., expansion) of the infarcted region (23,24). Hypertrophy is an independent risk factor for mortality and sudden death (25). Elevation of LV filling pressure at rest or during daily activities appears to contribute to global ventricular dilation, and remodeling (26) and may predispose to ventricular fibrillation by increasing dispersion of ventricular repolarization (27). Fibrosis may decrease electrical coupling and slow conduction velocity (27). The finding of the present study, that LV volume—a composite marker of remodeling—is significantly related to the development of arrhythmias while ejection fraction is not, may indicate that structural alterations are more closely related to the pathogenesis of arrhythmias than functional parameters. From this emerges the hypothesis that identification of LV dilation and remodeling, in concert with markers of electrical instability, should help identify patients at risk for sudden death. One may speculate that arrhythmias and the risk of sudden death may be reduced by therapeutic interventions aimed to attenuate LV remodeling. In fact, this study is historical with regard to the therapy of patients with LV dysfunction after MI. There is broad evidence that beta-adrenergic blocking agents and angiotensin-converting enzyme inhibitors may improve prognosis (28–30). The data presented may give some evidence of their complex mechanisms of action. In addition, the study suggests that the rigid search for LV dilation, dysfunction, arrhythmias and neurohumoral activation should be complementary in

studying patients for more intense therapy and follow-up. Progressive dilation should alert us to watch for life-threatening arrhythmias to prevent sudden death.

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Reprint requests and correspondence: Dr. Georg Ertl, Medizinische Universitätsklinik, Universität Würzburg, Josef-Schneider Strasse 2, 97080 Würzburg, Germany. E-mail: g.ertl@medizin.uni-wuerzburg.de.

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